Pharmacology & Pharmacy, **2013, 4, 115-120**
http://dx.doi.org/10.4236/pp.2013.41017 Published Online January 2013 (http://www.scirp.org/journal/pp)

The Pharmacogenomic Consideration of Lipid Homeostasis: Role of Pharmacist in Ethical and Economic Consideration

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Received November 20th, 2012; revised December 26th, 2012; accepted January 5th, 2013

ABSTRACT

Usage of lipid lowering drugs is a common therapeutic steps in preventing or treating diseases. With the advent of Pharmacogenetics and Pharmacogenomics, it is now important to understand the implication of pharmacogenetic testing in patient care. Ethical and economic concerns are wide considered to be an issue in a pharmacy setting and it is important that the health care professionals in the pharmacy setting need to be aware. This article encompasses current pharmacogenomic information that is relevant to lipid homeostasis and addressed the concerns of patient that may be a factor in ultimate decision making process.

Keywords: Pharmacogenomics; Lipid; Atherosclerosis; CVD; Pharmacogenetic Testing

1. Introduction

Little information is available when it comes to the personalization of medications. With that being said it was the inclination to provide a paper that discusses the idea of applying pharmacogenomics to the current lipid lowering therapies. Statins are the first line therapy for controlling lipid levels. Alternative therapies include cholesterol absorption inhibitors (ezetimibe), bile acid resins, fibrates and nicotinic acid. These medications are useful to keep lipid levels at a manageable level to decrease the risk for cardiovascular diseases. However, as with any medication, there are inherent differences between individuals to that effect the way a drug is absorbed, distributed, metabolized and eliminated. These processes ultimately influence the efficacy of treatment. This is where pharmacogenomics can be applied. Pharmacogenomics is the application of genetic variation to increase the efficacy of a drug. Pharmacogenomics can also be useful in identifying certain populations that would benefit from specific drug therapies. It takes the certain genetic differences amongst individuals into consideration to help optimize the drugs' potential as well as decrease toxic side effects.

Cholesterol is an important structural component of cell membranes in animal cells. It also proves to function in intracellular transport, cell signaling and nerve conduction. Cholesterol has been shown to be a precursor to many other biochemical pathways such as bile, vitamins and steroid hormones. Cholesterol levels in the body are regulated by a complex homeostatic system that is dependent on dietary sources of cholesterol. When intake is low, regulatory sensors are triggered that activate HMG-CoA reductase, a cholesterol-synthesizing enzyme, to seek out and convert plasma lipids into cholesterol. This enzyme is the rate-limiting step in cholesterol synthesis, and therefore a beneficial target for cholesterol-lowering therapy (**Figure 1** shows cholesterol pathway with target for statin therapy).

Cholesterol levels are divided into 5 measurable categories: very low density lipoproteins (VLDL), low density lipoproteins (LDL), high density lipoproteins (HDL), triglycerides (TG) and total cholesterol (TC). The efficacy of the pharmacologic agents on cholesterol are then

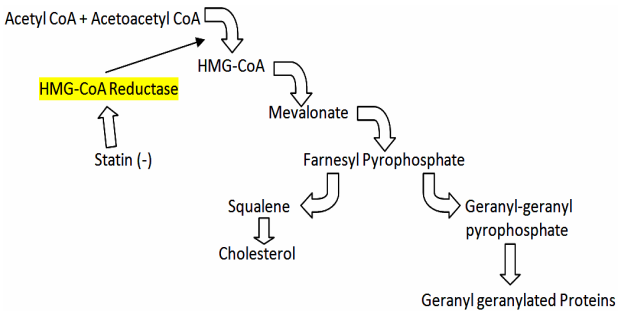

Figure 1. Schema of metabolic pathways involved in cholesterol biosynthesis and the target for lipid lowering drugs (statins).

determined based on their respective reduction or increase of these specific levels. The "bad" cholesterol that requires reduction is VLDL, LDL, TG and TC, while the "good" cholesterol that shows benefit when raised is HDL.

2. Target Genes

Medication efficacy and adverse effects are determined by the processes of absorption, distribution, metabolism and elimination. Genetic variation in these processes can then influence therapeutic response between individuals. Since statins are considered 1st line and are widely used, we start our discussion on how genes affect response with them.

For statin therapy, there are multiple candidate genes that can play a role in the efficacy and safety of drug treatment in terms of genetic variation. Statins work by selectively blocking cholesterol and isoprenoid biosynthesis by inhibition of HMG-CoA reductase (HMGCR). Therefore genetic mutations in the HMG-CoA reductase target site can lead to undesirable efficacy when statin therapy is initiated in an affected patient population. Another point for mutation can occur in metabolism of statins allowing for the drug to have a longer half-live than originally intended. One study identified 10 candidate genes involved in cholesterol synthesis that are worthy of genetic analysis. The targets identified with the most SNPs of the 10 candidate genes were HMGCR, LDLR, APOB and APOE [1]. Two other mutations occur on SLCO1B1 and KIF6 and have their distinct effect on statin metabolism and increased risk of CHD events, respectively.

2.1. HMGCR

Two SNPs that were identified within HMGCR effecting statin efficacy were SNP12 and SNP29 [1]. SNP12 was shown to have a decreasing effect on statin treatment when a single allele was expressed versus a homozygote for the wild type allele. No data was shown to prove it, but it would be assumed that a homozygote of the SNP12 allele would have a more pronounced decrease in statin therapy when compared to a single SNP12 allele. SNP29 demonstrated a similar effect on statin therapy. Both of these SNPs can be taken into account in that a higher initial dose may be warranted in patients that heterozygous or homozygous for either SNP12 or SNP29.

2.2. LDLR

Every nuclei-containing cell contains a LDL-Receptor (LDLR) that is responsible for binding LDL and then internalizing the lipoprotein for use by the cell. Mutations in the LDLR have been identified and are associated with higher propensity for familial hypercholesterolemia. Two mutations that have been associated with treatment resistant hypercholesterolemia are present on the gene for the LDLR [2]. Mutations in the LDLR are categorized as autosomal dominant hypercholesterolemia (ADH) [2]. Typical LDL levels are >200 mg/dl for a heterozygous ADH patient, and homozygotes can reach levels > 500 mg/dl [2]. This subset of hyperlipidemia expresses a great concern for the health of the patient, as well as the pill burden associated with its treatment. The two identified mutations are 2041T > Gly on exon 14 and IVS1-217C > T [2]. Both of these mutations are located on chromosome 19. The impact of the 204IG SNP is theorized to be enhanced by the IVS1-217T SNP. IVS1-217T is on the promoter region that is in *cis* with the exon 14 mutation, therefore increasing the expression of 2041TG [2]. This combination of SNP's increases the likelihood of treatment failure with conventional medications, forcing patients to undergo more extreme therapies.

2.3. ApoE & CETP

Apolipoprotein E (apoE) and cholesteryl ester transfer protein (CETP) are two targets that show variation in statin efficacy when SNPs are present. ApoE is made up of different isoforms with E2, E3 and E4 having increasing affinities for the LDL receptor [3]. E4 is associated with increased risk of atherosclerosis and cardiovascular mortality. These increased risks are due to statins decreased efficacy since there is less HMG-CoA synthesis associated with E4-carriers [3]. Therefore there is less of an available target for the statin to bind to. Conversely, E2-carriers show a benefit with statin therapy due to an increase in HMG-CoA synthesis. Not only has it been identified that E2-carriers respond better to statin therapy, but also that this may be gender specific, due to a greater reduction of male E2-carriers [3].

2.4. SLCOB1B1

One gene that plays a role in the adverse effect that is paramount of high dose statin therapy, rhabdomyolysis, is SLCOB1B1. This gene is part of a family of solute carriers that are known as membrane transport proteins. They consist of numerous carriers categorized into families and are responsible for facilitating transport of solutes either with or against concentration gradients. In the case of SLCO1B1, its role is summed up as regulation of statin uptake in the liver. When a SNP is present on this gene, it has been shown to increase the incidence of myopathy in a dose-dependent increment [4]. The SLCO1B1 gene is made up of 2 alleles, and risk of statin-induced myopathy is dependent on the specific SNP

that is displayed. Though there are many SNP's that can occur between the alleles for SLCO1B1, the rs4149056 SNP showed the greatest incidence of myopathy due to an association with increased blood levels of a statin [4]. Conversely, a rs2306283 allele was associated with lower statin blood levels and therefore decreased risk for myopathy. This decrease in blood levels will result in a lower efficacy for the statin treatment. This is an example of how pharmacogenetics can determine the severity of an adverse effect in a patient type.

2.5. KIF6

Another gene that plays a role in statin efficacy is KIF6. KIF6 is a kinesin like protein that is involved in intracellular transport of certain membrane-bound vesicles as well as proteins. Two SNP's have been identified in KIF6 that contribute to an increased risk for coronary heart disease [5]. The KIF6 gene can stray from the normal Trp/Trp alleles to either Arg/Trp or Arg/Arg, which are designated as KIF6 carriers [5]. Known carriers have been demonstrated to have an increased risk for CHD events. It is apparent that an Arg displayed on one of the KIF6 alleles can help identify an increased CHD event risk and need for initiating statin therapy sooner than is clinically acceptable. Data from the WOSCOPS, CARE, PROVE-IT-TIMI 22 and PROSPER trials have shown that aggressive statin therapy produced a greater reduction in CHD events for KIF6 carriers versus non-carriers [5].

2.6. MDR1

Other types of mutations that can affect the pharmacokinetics of lipid-lowering therapy have been identified in membrane transporters and metabolizing enzymes. MDR1 is a membrane associated protein responsible for transport of substrates across the cell membrane, such as medications. Medications that are substrates for this P-glycoprotein for transport are then subject to its effect. MDR1 is an ATP-dependent efflux pump that affects plasma levels of certain medications based on its expression. Two statin medications, lovastatin and atorvastin, show to be affected by the expression of MDR1 [6]. When MDR1 is over-expressed, it results in decreased drug levels due to the increase action of the efflux pump. Conversely, when MDR1 is under-expressed, it results in higher drug levels, which can then become toxic.

2.7. CYP3A4

Similar effects can be seen in the enzymes that metabolism medications. CYP-P450 is a family of enzymes that metabolize about 75% of current medications. Mutations in any of these enzymes can impact the metabolism and therefore affect both the efficacy and toxicity of the medication. CYP3A4 is a major part of the CYP-P450 family that accounts for an estimated 50% of metabolism of known drug therapies [7]. It has been demonstrated that mutations in CYP3A4 can have either a positive or negative effect on medication therapies. Mutations have been discovered in cytochrome P450 oxidoreductase (POR) that can affect drug efficacy through its metabolism. POR is an obligate electron donor for CYP3A4 and interacts with all 50 human microsomal P450 enzymes [7]. The mutation A287P is commonly found in Caucasians and resorts in a 75% loss of CYP3A4 metabolism. This result can be hypothesized to increase blood levels of drugs that are substrates of CYP3A4. Since POR mutation can have an effect on all P450 enzymes, it ultimately can affect any medication that using this pathway for metabolism. The effect of this interaction however cannot be determined because it varies depending on the geometry of the redox-partner binding site of the P450 [7]. These partners can vary from NADPH, NADH, FADH, etc.

2.8. APOA5

Fibrates are another cholesterol-lowering treatment that can be effected through genetic mutation. One such mutation has been demonstrated in apolipoprotein A5 (APOA5). When the variant in APOA5 of 56 G was expressed, it was correlated with increased efficacy of fenofibrate [8]. The wild type allele for APOA5 is 56 C. The mutant 56 G subtype, while associated with greater reduction in TG and increase in HDL with fenofibrate, is also associated with a higher level of TG and lower level of HDL compared to 56 C. This suggests that a carrier for 56 G would be a better candidate for fenofibrate therapy compared to a non-carrier. That non-carrier would then be tracked to a different type of lipid-lowering therapy.

2.9. GPR109A

GPR109A has recently been discovered to be the receptor to which nicotinic acid binds to in order to exert it anti-hyperlipidemic effect. It can be hypothesized that mutations in the gene that make up this receptor will have an effect on the affinity as to which nicotinic acid can bind. In my research I was unable to identify studies that dealt with the genetic implications regarding mutations in GPR109A.

2.10. NPC1L1

Neimann-Pick C1-Like1 (NPC1L1) has been identified as the molecular target for ezetimibe in order to exert its cholesterol-lowering effects [9]. It is present in the brush

border membrane of the intestines. It can be hypothesized the mutations that effect the expressions of this gene will affect the efficacy of ezetimibe. In my research I was unable to identify studies that dealt with the genetic implications regarding mutations in NPC1L1.

2.11. Bile Acid Sequestrants

As is indicated in the name, bile acid sequestrants such as cholestyramine require that bile is produced so that it can then be excreted from the body. It can be hypothesized that if there are mutations in the pathway that involve the synthesis of bile that halt this process, the bile acid sequestrant will be of no use. In my research I was unable to identify possible SNPs that would alter the efficacy of bile acid sequestrants.

3. Clinical Applications

Discovery of these mutations and the effect they can carry is well, but the importance lies in the application of this information. Specific lipid-lowering therapies can be selected for patients who are identified as carrier-types for affecting SNPs. It is a noble idea to think that once a patient has been genotyped, only efficient medications and dose with the least amount of adverse effects can be allotted for that patient. However since pharmacogenomics is still an advancing science, there is a lack of commercially available tests for all SNPs that can play a significant role in lipid-lowering therapies. There are some tests that are available to assist healthcare professionals in selecting viable therapies in the treatment of hyperlipidemia.

Now that a SNP in the SLCO1B1 gene can be associated with changes in drug efficacy as well as adverse effects, it can be used to optimize the application of the statin. Those patients who have the rs4149056 SNP can be applied a limited amount of a statin dose to decrease the risk of developing rhabdomyolysis. While those patients who are identified as having the rs230683 SNP can initially be started on a higher statin dose since they don't retain as high of blood levels of the drug. However, the efficacy of personalizing a therapy is dependent on identification of the SNP. Most patients who are candidates for statin treatment are not going to be genotyped and sequenced to identify if they carry the SNP's responsible for adverse statin treatments. Single tests to identify the pertinent SNPs are not all commercially available. These tests can be very expensive, especially when it comes to complete genotype sequencing. It is estimated to be around $50,000 for a whole human genome and can take around 4 weeks to complete, as of 2009 [10]. It should certainly be assumed that this cost has decreased since 2009, and will continue to drop as newer, faster techniques are developed.

When a KIF6 carrier is identified, it has been shown that intensive statin therapy has an increased benefit in reducing CHD events than in non carriers. Three studies (WOSCOPS, CARE and PROVE-IT) who differentiated between KIF6 carrier and non-carrier displayed more than a 30% reduction in relative risk for CHD events for the carrier group when given intensive statin therapy [5]. The relative reduction in risk for the non-carrier group was 20% or less respectively. This data shows a great need for identification of KIF6 carriers so that appropriate statin therapy can then be initiated. Identification can be done through the KIF6-StatinCheck™ Genotype Test [5]. This test kit ranges from $20 to $152 depending on insurance coverage. Therefore it is relatively inexpensive to perform while the benefits of identification can greatly influence treatment outcome.

Other commercially available tests offer the option to genotype one's metabolism and the SNPs that can be encountered. One such test is called the Taqman® Drug Metabolism Genotyping Assay. This test identifies SNPs in the metabolism pathways of medications. Having knowledge of drug metabolism, a pharmacist or other health professional could then determine what dose of what medication would be best for a patient. The results from this test can then be applied to practice by then selecting medications that avoid or take advantage of patient-specific SNPs.

4. Ethics/Legality/Cost-Effectiveness

4.1. Ethics

Patients put trust into health care providers in that their medical information is kept private. With genetic testing becoming more available, concern with how this information is handled grows. As easy as it is to see someone and judge them based on appearance, it can be just as easy for patients to be judged based on their genotypes. Who is allowed to see this information is an issue that needs to be investigated in great detail. Insurance companies can deem certain patient subtypes uninsurable if they have genetic predisposition for expensive diseases. Besides this issue, another arises with the possibility of a social stigma being cast on patient subtypes. This information needs to remain confidential and used appropriately so that it can provide benefit to the patient.

Another important ethical issue concerning pharmacogenetics is the availability to patients. The expense of some tests may limit their use to a higher socioeconomic status. It is ethical to say that testing should be made available to all socioeconomic classes. Should it be the role of the manufacturer not to expect a profit from the years of research and resources put into developing ge-

netic testing? These and other ethical issues need to be explored so that pharmacogenetics can be applied to its best.

4.2. Legality

With the adaptation of pharmacogenetic testing into clinical practice, new laws need to be made that pertain to this newly developed setting. As was mentioned earlier with patient confidentiality, medical records that hold information regarding genetic information need to remain private. This information holds great impact on not only the insurability of an individual, but also the employability. Guidelines need to be laid out that offer a protocol on who, when and how genetic information can be utilized. Patients should also be informed about the impact genetic testing can have, both beneficial and negative.

4.3. Cost-Effectiveness

Cost is an important issue to many people especially when it comes to medical therapies. Often people will neglect their health if they can't afford a medication they were prescribed. There are limited trials demonstrating the cost-effectiveness that pharmacogenetic application can have. With that being said concerns arise about whether the effect of genetic testing is worth the cost. Will it really change the outcome of a patient's health for the better, or will the benefit be too small to measure? Also genetic testing may only benefit a small population that has a high mortality rate. If this is the case, the effect may be great in that it saves lives, but the cost will be equally as high and perhaps unaffordable.

5. Role of Healthcare Professionals

Risk verse benefits. This is the ultimate question that needs to be answered to justify whether genetic testing should be a regular practice associated with drug therapy. Healthcare practitioners have a role to fill when it comes to genetic testing. Since they are directly involved in the health of individuals, they are able to help educate them on the necessity of performing a genetic test or not. They can also relay the benefits that may be associated with certain testing for SNP's that can play a role in their drug regimen.

Pharmacist's have a unique role when it comes to genetic testing and its results. Since they are easily accessible, it is important for pharmacists as well as other healthcare professionals to stay up-to-date in the latest technology. They are the median that can bridge the gap between the science of pharmacogenetics and the public. Providing an educated input on the pros and cons of undergoing genetic testing can offer an optimal benefit for the patient. Consumers are able to purchase some genetic testing kits online, and therefore are subject to interpreting the results themselves. Pharmacists being the most available healthcare professional for the public need to stay educated on this advancing science so they are prepared when approached with questions.

Since pharmacogenetics is still an advancing science, some healthcare professionals may be wary of utilizing its benefits in their practice. Evidence needs to be made available to the healthcare professional that proves the efficacy behind the application of pharmacogenetics to medication management. The ultimate beneficiary of this important science is the patient, so the healthcare professional needs to take this in mind. The only way the patient can receive personalized medication therapy is for the physician or pharmacist to have developed a background in pharmacogenetics and its application. So continual education on advancing topics in healthcare needs to be a major component of practice.

REFERENCES

[1] D. J. Chasman, D. Posada, L. Subrahmanyan, N. R. Cook, V. P. Stanton Jr. and P. M. Ridker, "Pharmacogenetic Study of Statin Therapy and Cholesterol Reduction," *JAMA*, Vol. 291, No. 23, 2004, pp. 2821-2827.

[2] C. L. Snozek, *et al*., "LDLR Promoter Variant and Exon 14 Mutation on the Same Chromosome Are Associated with an Unusually Severe FH Phenotype and Treatment Resistance," *European Journal of Human Genetics*, Vol. 17, No. 1, 2009, pp. 85-89. doi:10.1038/ejhg.2008.199

[3] G. Schmitz and T. Langmann, "Pharmacogenomics of Cholesterol-Lowering Therapy," *Vascular Pharmacology*, Vol. 44, 2006, pp. 75-89. doi:10.1016/j.vph.2005.07.012

[4] The SEARCH Collaborative Group, "SLCO1B1 Variants and Statin-Induced Myopathy—A Genomewide Study," *The New England Journal of Medicine*, Vol. 359, No. 8, 2008, pp. 789-799.

[5] Celera Advertisement, "KIF6-StatinCheck Genotype Test," Heartlab, Berkeley, 2010.

[6] T. Sakaeda, T. Nakamura and K. Okumura, "MDR1 Genotype-Related Pharmacokinetics and Pharmacodynamics," *Biological & Pharmaceutical Bulletin*, Vol. 25, No. 11, 2002, pp. 1391-1400.

[7] E. F. Christa, P. E. Mullis and A. V. Pandey, "Reduction in Hepatic Drug Metabolizing CYP3A4 Activities Caused by P450 Oxidoreductase Mutations Identified in Patients with Disordered Steroid Metabolism," *Biochemical and Biophysical Research Communications*, Vol. 401, No. 1, 2010, pp. 149-153.

[8] C. Q. Lai, D. K. Arnett, D. Corella, R. J. Straka, M. Y. Tsai, J. M. Peacock, X. Adiconis, L. D. Parnell, J. E. Hixson, *et al*., "Fenofibrate Effect on Triglyceride and Postprandial Response of Apolipoprotein A5 Variants, The GOLDN Study," *Arteriosclerosis, Thrombosis, and Vascular Biology*, Vol. 27, No. 6, 2007, pp. 1417-1425.

[9] M. J. Garcia-Calvo, J. Lisnock, H. G. Bull, *et al*., "The Target of Ezetimibe Is Niemann-Pick C1-Like 1 (NPC1L1)," *Proceedings of the National Academy of Sciences*, Vol. 102, No. 23, 2005, pp. 8132-8137.

[10] W. Nicholas, "Cost of Decoding a Genome Is Lowered," *The New York Times*, 11 August 2009.

